AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph beginning at page 2, line 12 with the following amended paragraph.

~~Any~~ The invention provides for an isolated or purified nucleic acid polynucleotide that codes for a protease capable of cleaving the beta (β) secretase cleavage site of APP that contains two or more sets of special nucleic acids, where the special nucleic acids are separated by nucleic acids that code for about 100 to 300 amino acid positions, where the amino acids in those positions may be any amino acids, where the first set of special nucleic acids consists of the nucleic acids that code for the peptide DTG, where the first nucleic acid of the first special set of nucleic acids is, the first special nucleic acid, and where the second set of nucleic acids code for either the peptide DSG or DTG, where the last nucleic acid of the second set of nucleic acids is the last special nucleic acid, with the proviso that the nucleic acids disclosed in SEQ ID NO. 1 and SEQ. ID NO. 5 are not included. ~~The nucleic acid polynucleotide of claim 1 where the~~ In one embodiment, the two sets of nucleic acids are separated by nucleic acids that code for about 125 to 222 amino acid positions, which may be any amino acids. ~~The nucleic acid polynucleotide of claim 2~~ In a particular embodiment, the two sets of special nucleic acids are separated by nucleic acids that code for about 150 to 172 amino acid positions, which may be any amino acids. ~~The nucleic acid polynucleotide of claim~~ In a more particular embodiment, the two sets are separated by nucleic acids that code for about 172 amino acid positions, which may be any amino acids. An exemplary ~~The nucleic acid~~ polynucleotide ~~of claim 4 where~~ comprises the ~~nucleotides are~~ nucleic acid described in SEQ. ID. NO. 3. In another embodiment, ~~The nucleic acid polynucleotide of claim 2 where~~ the two sets of nucleic acids are separated by nucleic acids that code for about 150 to 196 amino acid positions. ~~The nucleic acid polynucleotide of claim 6 where~~ In another embodiment, the two sets of nucleotides are separated by nucleic acids that code for about 196 amino acids ~~(positions)~~. ~~The nucleic acid~~ An exemplary polynucleotide ~~of claim 7 where~~ comprises the two sets of nucleic acids ~~are~~ separated by the same nucleic acid sequences that separate the same set of special nucleic acids in SEQ. ID. NO. 5. The ~~nucleic acid polynucleotide of claim 4where the~~ In a particular embodiment, the two sets of nucleic acids are separated by nucleic acids that code for about 150 to 190, amino acid ~~(positions)~~. ~~The nucleic acid polynucleotide of claim 9 where~~ In another embodiment,

the two sets of nucleotides are separated by nucleic acids that code for about 190 amino acids ~~(positions)~~. ~~The nucleic acid polynucleotide of claim 10 where~~ In a more particular embodiment, the two sets of nucleotides are separated by the same nucleic acid sequences that separate the same set of special nucleotides in SEQ. ID. NO. 1. ~~Claims 1-11 where~~ In one embodiment, the first nucleic acid of the first special set of amino acids, that is, the first special nucleic acid, is operably linked to any codon where the ~~nuclie~~ nucleic acids of that codon codes for any peptide comprising from 1 to 10,000 amino acid ~~(positions)~~. ~~The nucleic acid polynucleotide of claims 1-12 where~~ In one variation, the first special nucleic acid is operably linked to nucleic acid polymers that code for any peptide selected from the group consisting of: any any reporter proteins or proteins which facilitate purification. ~~The nucleic acid polynucleotide of claims 1-13 where~~ In another variation, the first special nucleic acid is operably linked to nucleic acid polymers that code for any peptide selected from the group consisting of: immunoglobin-heavy chain, maltose binding protein, glutathion S transfection, Green Fluorescent protein, and ubiquitin. ~~Claims 1-14 where~~ In another embodiment, the last nucleic acid of the second set of special amino acids, that is, the last special nucleic acid, is operably linked to nucleic acid polymers that code for any peptide comprising any amino acids from 1 to 10,000 amino acids. ~~Claims 1-15 where~~ In one variation, the last special nucleic acid is operably linked to any codon linked to nucleic acid polymers that code for any peptide selected from the group consisting of: any reporter proteins or proteins which facilitate purification. ~~The nucleic acid polynucleotide of claims 1-16 where~~ In another embodiment, the first special nucleic acid is operably linked to nucleic acid polymers that code for any peptide selected from the group consisting of: immunoglobin-heavy chain, maltose binding protein, glutathion S transfection, Green Fluorescent protein, and ubiquitin.

Please replace the paragraph beginning at page 3, line 25 with the following amended paragraph.

~~Any~~ The invention provides for an isolated or purified nucleic acid polynucleotide that codes for a protease capable of cleaving the beta secretase cleavage site of APP that contains two or more sets of special nucleic acids, where the special nucleic acids are separated by nucleic acids that code for about 100 to 300 amino acid positions, where the

amino acids in those positions may be any amino acids, where the first set of special nucleic acids consists of the nucleic acids that code for DTG, where the first nucleic acid of the first special set of nucleic acids is, the first special nucleic acid, and where the second set of nucleic acids code for either DSG or DTG, where the last nucleic acid of the second set of special nucleic acids is the last special nucleic acid, where the first special nucleic acid is operably linked to nucleic acids that code for any number of amino acids from zero to 81 amino acids and where each of those codons may code for any amino acid. ~~The nucleic acid polynucleotide of claim 18, where~~ In an embodiment, the first special nucleic acid is operably linked to nucleic acids that code for any number of from 64 to 77 amino acids where each codon may code for any amino acid. ~~The nucleic acid polynucleotide of claim 19, where~~ In a particular embodiment, the first special nucleic acid is operably linked to nucleic acids that code for 71 amino acids. ~~The nucleic acid polynucleotide of claim 20, where~~ For example, the first special nucleic acid is operably linked to 71 amino acids and where the first of those 71 amino acids is the amino acid T. ~~The nucleic acid polynucleotide of claim 21, where~~ In another embodiment, the polynucleotide comprises a sequence that is at least 95% identical to ~~SEQ. ID. (Example 11)~~ a human Asp1 or Asp2 sequence as taught herein. ~~The nucleic acid polynucleotide of claim 22, where the complete polynucleotide comprises SEQ. ID. (Example 11). The nucleic acid polynucleotide of claim 18, where~~ In still another embodiment, the first special nucleic acid is operably linked to nucleic acids that code for any number of from 40 to 54 amino acids where each codon may code for any amino acid. ~~The nucleic acid polynucleotide of claim 24, where~~ In a particular embodiment, the first special nucleic acid is operably linked to nucleic acids that code for 47 amino acids. ~~The nucleic acid polynucleotide of claim 20, where~~ For example, the first special nucleic acid is operably linked to 47 codons where the first those 47 amino acids is the amino acid E. ~~The nucleic acid polynucleotide of claim 21, where the~~ such as a polynucleotide ~~comprises~~ comprising a sequence that is at least 95% identical to SEQ. ID. NO: 29 described in Example 10 or ~~(Example 10). The nucleic acid polynucleotide of claim 22, where~~ the complete polynucleotide sequence of ~~comprises~~ SEQ. ID. NO: 29 described in Example 10. ~~(Example 10).~~

Please replace the paragraph beginning at page 4, line 21 with the following amended paragraph.

~~Any~~ In another related aspect, the invention provides for an isolated or purified nucleic acid polynucleotide that codes for a protease capable of cleaving the beta (β) secretase cleavage site of APP that contains two or more sets of special nucleic acids, where the special nucleic acids are separated by nucleic acids that code for about 100 to 300 amino acid positions, where the amino acids in those positions may be any amino acids, where the first set of special nucleic acids consists of the nucleic acids that code for the peptide DTG, where the first nucleic acid of the first special set of amino acids is, the first special nucleic acid, and where the second set of special nucleic acids code for either the peptide DSG or DTG, where the last nucleic acid of the second set of special nucleic acids, the last special nucleic acid, is operably linked to nucleic acids that code for any number of codons from 50 to 170 codons. ~~The nucleic acid polynucleotide of claim 29 where~~ In an embodiment, the last special nucleic acid is operably linked to nucleic acids comprising from 100 to 170 codons. ~~The nucleic acid polynucleotide of claim 30 where~~ In a particular embodiment, the last special nucleic acid is operably linked to nucleic acids comprising from 142 to 163 codons. ~~The nucleic acid polynucleotide of claim 31 where~~ In another embodiment, the last special nucleic acid is operably linked to nucleic acids comprising about 142 codons. ~~The nucleic acid polynucleotide of claim 32 where~~ For example, the polynucleotide comprises a sequence that is at least 95% identical to SEQ. ID NO: 21 described in Example 9 or SEQ ID NO: 29 described in Example 10 or ~~(Example 9 or 10)The nucleic acid polynucleotide of claim 33, where~~ the complete polynucleotide sequence of ~~comprises~~ SEQ. ID. NO: 21 described in Example 9 or SEQ ID NO: 29 described in Example 10. ~~(Example 9 or 10). The nucleic acid polynucleotide of claim 31 where~~ In one variation, the last special nucleic acid is operably linked to nucleic acids comprising about 163 codons. ~~The nucleic acid polynucleotide of claim 35 where the polynucleotide comprises a sequence that is at least 95% identical to SEQ. ID. (Example 9 or 10). The nucleic acid polynucleotide of claim 36, where the complete polynucleotide comprises SEQ. ID. (Example 9 or 10). The nucleic acid polynucleotide of claim 31 where~~ In another variation, the last special nucleic acid is operably linked to nucleic acids comprising about 170 codons. ~~Claims 1-38 where~~ In another embodiment, the second set of special ~~nucleid~~ nucleic acids code for the peptide DSG, and optionally the first set of nucleic acid polynucleotide is operably linked to a peptide

purification tag. ~~Claims 1-39 where~~ For example, the nucleic acid polynucleotide is operably linked to a peptide purification tag which is six histidine. ~~Claims 1-40 where~~ In still another embodiment, the first set of special nucleic acids are on one polynucleotide and the second set of special nucleic acids are on a second polynucleotide, where both first and second polynucleotides have at lease 50 codons. ~~Claims 1-40 where~~ In one embodiment of this type, the first set of special nucleic acids are on one polynucleotide and the second set of special nucleic acids are on a second polynucleotide, where both first and second polynucleotides have at lease 50 codons where both said polynucleotides are in the same solution. ~~A~~ In a related aspect, the invention provides for a vector which contains a polynucleotide as described above ~~in claims 1-42. A~~, and a cell or cell line which ~~contans~~ contains a polynucleotide described above ~~in claims 1-42~~.

Please replace the paragraph beginning at page 5, line 24 with the following amended paragraph.

~~Any~~ In still another aspect, the invention provides an isolated or purified peptide or protein comprising an amino acid polymer that is a protease capable of cleaving the beta (β) secretase cleavage site of APP that contains two or more sets of special amino acids, where the special amino acids are separated by about 100 to 300 amino acid positions, where each amino acid position can be any amino acid, where the first set of special amino acids consists of the peptide DTG, where the first amino acid of the first special set of amino acids is, the first special amino acid, where the second set of amino acids is selected from the peptide comprising either DSG or DTG, where the last amino acid of the second set of special amino acids is the last special amino acid, with the proviso that the proteases disclosed in SEQ ID NO. 2 and SEQ. ID NO. 6 are not included. ~~The amino acid polypeptide of claim 45 where~~ In an embodiments, the two sets of amino acids are separated by about 125 to 222 amino acid positions where in each position it may be any amino acid. ~~The amino acid polypeptide of claim 46 where~~ In a particular embodiment, the two sets of amino acids are separated by about 150 to 172 amino acids. ~~The amino acid polypeptide of claim 47 where~~ In another particular embodiment, the two sets of amino acids are separated by about 172 amino acids. ~~The amino acid polypeptide of claim 48 where~~ For example, the polypeptide is a the protease ~~is~~ described in SEQ. ID. NO. 4 ~~The amino acid polypeptide of~~

~~claim 46 where~~ In another particular embodiment, the two sets of amino acids are separated by about 150 to 196 amino acids. ~~The amino acid polypeptide of claim 50 where~~ In one variation, the two sets of amino acids are separated by about 196 amino acids. ~~The amino acid polypeptide of claim 51 where~~ In an embodiment, the two sets of amino acids are separated by the same amino acid sequences that separate the same set of special amino acids in SEQ. ID. NO. 6. ~~The amino acid polypeptide of claim 46 where~~ In a particular embodiment, the two sets of amino acids are separated by about 150 to 190, amino acids. ~~The amino acid polypeptide of claim 53 where~~ In another particular embodiment, the two sets of nucleotides are separated by about 190 amino acids. ~~The amino acid polypeptide of claim 54 where~~ For example, the two sets of nucleotides are separated by the same amino acid sequences that separate the same set of special amino acids in SEQ. ID. NO. 2. ~~Claims 45-55 where~~ In one embodiment, the first amino acid of the first special set of amino acids, that is, the first special amino acid, is operably linked to any peptide comprising from 1 to 10,000 amino acids. ~~The amino acid polypeptide of claims 45-56 where~~ In another embodiment, the first special amino acid is operably linked to any peptide selected from the group consisting of: any any reporter proteins or proteins which facilitate purification. ~~The amino acid polypeptide of claims 45-57 where~~ In particular embodiments, the first special amino acid is operably linked to any peptide selected from the group consisting of: immunoglobin-heavy chain, maltose binding protein, glutathion S transfection, Green Fluorescent protein, and ubiquitin. ~~Claims 45-58, where~~ In still another variation, the last amino acid of the second set of special amino acids, that is, the last special amino acid, is operably linked to any peptide comprising any amino acids from 1 to 10,000 amino acids. ~~Claims 45-59 where~~ By way of nonlimiting example, the last special amino acid is operably linked any peptide selected from the group consisting of any reporter proteins or proteins which facilitate purification. ~~The amino acid polypeptide of claims 45-60 where~~ In particular embodiments, the first special amino acid is operably linked to any peptide selected from the group consisting of: immunoglobin-heavy chain, maltose binding protein, glutathion S transfection, Green Fluorescent protein, and ubiquitin.

Please replace the paragraph beginning at page 6, line 31 with the following amended paragraph.

~~Any~~ The invention also provides for an isolated or purified peptide or protein comprising an amino acid polypeptide that codes for a protease capable of cleaving the beta secretase cleavage site of APP that contains two or more sets of special amino acids, where the special amino acids are separated by about 100 to 300 amino acid positions, where each amino acid in each position can be any amino acid, where the first set of special amino acids consists of the amino acids DTG, where the first amino acid of the first special set of amino acids is, the first special amino acid, D, and where the second set of amino acids is either DSG or DTG, where the last amino acid of the second set of special amino acids is the last special amino acid, G, where the first special amino acid is operably linked to amino acids that code for any number of amino acids from zero to 81 amino acid positions where in each position it may be any amino acid. ~~The amino acid polypeptide of claim 62, where~~ In one embodiment, the first special amino acid is operably linked to a peptide from about 64 to 77 amino acids positions where each amino acid position may be any amino acid. ~~The amino acid polypeptide of claim 63, where~~ In a particular embodiment, the first special amino acid is operably linked to a peptide of 71 amino acids. ~~The amino acid polypeptide of claim 64, where~~ In a more particular embodiment, the first special amino acid is operably linked to 71 amino acids and the first of those 71 amino acids is the amino acid T. ~~The amino acid polypeptide of claim 65, where~~ For example, the polypeptide comprises a sequence that is at least 95% identical to ~~SEQ. ID. (Example 11)~~ an aspartyl protease sequence as described herein. ~~The amino acid polypeptide of claim 66, where the complete polypeptide comprises SEQ. ID. (Example 11).~~ ~~The amino acid polypeptide of claim 62, where~~ In another embodiment, the first special amino acid is operably linked to any number of from 40 to 54 amino acids ~~(positions)~~ where each amino acid position may be any amino acid. ~~The amino acid polypeptide of claim 68, where~~ In a particular embodiment, the first special amino acid is operably linked to amino acids that code for a peptide of 47 amino acids. ~~The amino acid polypeptide of claim 69, where~~ In a very particular embodiment, the first special amino acid is operably linked to a 47 amino acid peptide where the first those 47 amino acids is the amino acid E. ~~The amino acid polypeptide of claim 70, where~~ For example, the polypeptide comprises a sequence that is at least 95% identical to SEQ. ID. NO: 30 described in Example

10 or ~~(Example 10). The amino acid polypeptide where the~~ or the complete polypeptide sequence of SEQ ID NO: 30 described in ~~comprises~~ Example 10[[)]].

Please replace the paragraph beginning at page 7, line 25 with the following amended paragraph.

~~Any~~ In still another related aspect, an isolated or purified amino acid polypeptide that is a protease capable of cleaving the beta (β) secretase cleavage site of APP that contains two or more sets of special amino acids, where the special amino acids are separated by about 100 to 300 amino acid positions, where each amino acid in each position can be any amino acid, where the first set of special amino acids consists of the amino acids that code for DTG, where the first amino acid of the first special set of amino acids is, the first special amino acid, D, and where the second set of amino acids are either DSG or DTG, where the last amino acid of the second set of special amino acids is the last special amino acid, G, which is operably linked to any number of amino acids from 50 to 170 amino acids, which may be any amino acids. ~~The amino acid polypeptide of claim 73 where~~ In one embodiment, the last special amino acid is operably linked to a peptide of about 100 to 170 amino acids. ~~The amino acid polypeptide of claim 74 where~~ In a particular embodiment, the last special amino acid is operably linked to to a peptide of about 142 to 163 amino acids. ~~The amino acid polypeptide of claim 75 where~~ In another particular embodiment, the last special amino acid is operably linked to to a peptide of about about 142 amino acids. ~~The amino acid polypeptide of claim 76 where~~ For example, the polypeptide comprises a sequence that is at least 95% identical to SEQ. ID. NO: 22 described in Example 9 or SEQ ID NO: 30 described in Example 10. ~~(Example 9 or 10) The amino acid polypeptide of claim 75 where~~ In one particular embodiment, the last special amino acid is operably linked to a peptide of about 163 amino acids. ~~The amino acid polypeptide of claim 79 where~~ For example, the polypeptide comprises a sequence that is at least 95% identical to SEQ. ID. NO: 22 described in Example 9 or SEQ ID NO: 30 described in Example 10, or ~~(Example 9 or 10). The amino acid polypeptide of claim 79, where~~ the complete polypeptide sequence of ~~comprises~~ SEQ. ID. NO: 22 described in Example 9 or SEQ ID NO: 30 described in Example 10. ~~(Example 9 or 10).~~ The amino acid polypeptide of claim 74 where In another embodiment, the last special amino acid is operably linked to to a peptide of about 170 amino

acids. ~~Claim 46-81 where~~ In a particular embodiment, the second set of special amino acids is comprised of the peptide with the amino acid sequence DSG. ~~Claims 45-82 where~~ Optionally, the amino acid polypeptide is operably linked to a peptide purification tag. ~~Claims 45-83 where the amino acid polypeptide is operably linked to~~ such as a peptide purification tag which is six histidine. ~~Claims 45-84 where~~ In one variation, the first set of special amino acids are on one polypeptide and the second set of special amino acids are on a second polypeptide, where both first and second polypeptide have at lease 50 amino acids, which may be any amino acids. ~~Claims 45-84 where~~ In another variation, the first set of special amino acids are on one polypeptide and the second set of special amino acids are on a second polypeptide, where both first and second polypeptides have at lease 50 amino acids where both said polypeptides are in the same vessel. The invention also provides for a ~~A~~ vector which contains a polypeptide ~~described in claims 45-86~~ as described herein. ~~A~~ The invention further provides for a cell or cell line which ~~contans~~ contains a polynucleotide described ~~in claims 45-87~~ herein. The invention also provides for a ~~The~~ process of making any of the polynucleotides, vectors, or cells ~~of claims 1-44~~ described herein, and a ~~The~~ process of making any of the polypeptides~~, vectors or cells of claims 45-88~~ described herein. ~~Any of the polynucleotides, polypeptides, vectors, cells or cell lines described in claims 1-88 made from the processes described in claims 89 and 90.~~

Please replace the paragraph beginning at page 9, line 7 with the following amended paragraph.

The invention provides for an amino acid polypeptide ~~of claim 62~~ described herein, where the first special amino acid is operably linked to a peptide from about 30 to 77 amino acids positions where each amino acid position may be any amino acid. The invention also provides for an amino acid polypeptide ~~of claim 63~~ described herein, where the first special amino acid is operably linked to a peptide of 35, 47, 71, or 77 amino acids.

Please replace the paragraph beginning at page 9, line 11 with the following amended paragraph.

The invention provides for an amino acid polypeptide ~~of claim 63~~ described herein, where the first special amino acid is operably linked to the same corresponding

peptides from SEQ. ID. NO. 3 that are 35, 47, 71, or 77 peptides in length, beginning counting with the amino acids on the first special sequence, DTG, towards the N-terminal of SEQ. ID. NO. 3.

Please replace the paragraph beginning at page 9, line 15 with the following amended paragraph.

The invention provides for an amino acid polypeptide ~~of claim 65~~ described herein, where the polypeptide comprises a sequence that is at least 95% identical to the same corresponding amino acids in SEQ. ID. NO. 4, that is, identical to that portion of the sequences in SEQ.ID. NO. 4, including all the sequences from both the first and or the second special nucleic acids, toward the N- terminal, through and including 71, 47, 35 amino acids before the first special amino acids. (Examples 10 and 11).

Please replace the paragraph beginning at page 9, line 21 with the following amended paragraph.

The invention provides for an amino acid polypeptide ~~of claim 65~~ described herein, where the complete polypeptide comprises the peptide of 71 amino acids, where the first of the amino acid is T and the second is Q. The invention also provides for a nucleic acid polynucleotide ~~of claim 21~~ described herein, where the polynucleotide comprises a sequence that is at least 95% identical to the same corresponding amino acids in SEQ. ID. NO. 3, that is, identical to the sequences in SEQ. ID. NO. 3 including the sequences from both the first and or the second special nucleic acids, toward the N-Terminal, through and including 71 amino acids, see Example 10, beginning from the DTG site and including the nucleotides from that code for 71 amino acids).

Please replace the paragraph beginning at page 9, line 29 with the following amended paragraph.

The invention provides for a nucleic acid polynucleotide ~~of claim 22~~ described herein, where the complete polynucleotide comprises identical to the same corresponding amino acids in SEQ. ID. NO. 3, that is, identical to the sequences in SEQ. ID. NO. 3

including the sequences from both the first and or the second special nucleic acids, toward the N-Terminal, through and including 71 amino acids, see Example 10, beginning from the DTG site and including the nucleotides from that code for 71 amino acids).

Please replace the paragraph beginning at page 10, line 3 with the following amended paragraph.

The invention provides for a nucleic acid polynucleotide ~~of claim 18~~ described herein, where the first special nucleic acid is operably linked to nucleic acids that code for any number of from about 30 to 54 amino acids where each codon may code for any amino acid.

Please replace the paragraph beginning at page 10, line 6 with the following amended paragraph.

The invention provides for a nucleic acid polynucleotide ~~of claim 20~~ described herein, where the first special nucleic acid is operably linked to 47 codons where the first those 35 or 47 amino acids is the amino acid E or G.

Please replace the paragraph beginning at page 10, line 9 with the following amended paragraph.

The invention provides for a nucleic acid polynucleotide ~~of claim 21~~ described herein, where the polynucleotide comprises a sequence that is at least 95% identical to the same corresponding amino acids in SEQ. ID. NO. 3, that is, identical to that portion of the sequences in SEQ. ID. NO. 3 including the sequences from both the first and or the second special nucleic acids, toward the N-Terminal, through and including 35 or 47 amino acids, see Example 11 for the 47 example, beginning from the DTG site and including the nucleotides from that code for the previous 35 or 47 amino acids before the DTG site [[)]] The nucleic acid polynucleotide ~~of claim 22~~ of the present invention, where the polynucleotide comprises identical to the same corresponding amino acids in SEQ. ID. NO. 3, that is, identical to the sequences in SEQ. ID. NO. 3 including the sequences from both the first and or the second special nucleic acids, toward the N-Terminal, through and including

35 or 47 amino acids, see Example 11 for the 47 example, beginning from the DTG site and including the nucleotides from that code for the previous 35 or 47 amino acids before the DTG site[[)]].

Please replace the paragraph beginning at page 10, line 31 with the following amended paragraph.

The invention provide for a nucleic acid molecule ~~of claim 92~~, wherein said Hu-Asp polypeptide is Hu-Asp1, and said polynucleotide molecule ~~of 1(a)~~ comprises the nucleotide sequence of SEQ ID ~~No.~~ NO:1; and a ~~The~~ nucleic acid molecule ~~of claim 92~~, wherein said Hu-Asp polypeptide is Hu-Asp2(a), and said polynucleotide molecule ~~of 1(a)~~ comprises the nucleotide sequence of ~~SEQ ID No. 4~~ SEQ ID NO: 3; and a ~~The~~ nucleic acid molecule ~~of claim 92, wherein said~~ that encodes a Hu-Asp polypeptide that is Hu-Asp2(b), and said polynucleotide molecule ~~of 1(a)~~ comprises the nucleotide sequence of SEQ ID No. 5. The invention provides for an ~~An~~ isolated nucleic acid molecule comprising polynucleotide which hybridizes under stringent conditions to a polynucleotide having the nucleotide sequence ~~in (a) or (b) of claim 92~~ described above. The invention also provides for a ~~A~~ vector comprising the nucleic acid molecule ~~of claim 96~~ described herein. Optionally, the ~~The~~ vector ~~of claim 97, wherein said~~ contains a nucleic acid molecule ~~is~~ operably linked to a promoter for the expression of a Hu-Asp polypeptide such as ~~The vector of claim 98, wherein said Hu-Asp polypeptide is~~ Hu-Asp1, ~~The vector of claim 98, wherein said Hu-Asp polypeptide is~~ Hu-Asp2(a) or ~~The vector of claim 98, wherein said Hu-Asp polypeptide is~~ Hu-Asp2(b). The invention provides for a ~~A~~ host cell comprising the vector ~~of claim 98~~ described above. The invention also provides for a ~~A~~ method of obtaining a Hu-Asp polypeptide comprising culturing the host cell ~~of claim 102~~ described above and isolating said Hu-Asp polypeptide. The invention provides for an ~~An~~ isolated Hu-Asp1 polypeptide comprising an amino acid sequence at least 95% identical to a sequence comprising the amino acid sequence of SEQ ID No. 2, an ~~An~~ isolated Hu-Asp2(a) polypeptide comprising an amino acid sequence at least 95% identical to a sequence comprising the amino acid sequence of SEQ ID No. 4, and an ~~An~~ isolated Hu-Asp2(a) polypeptide comprising an amino acid sequence at least 95% identical to a sequence comprising the amino acid sequence of SEQ ID No. 8. The invention also provides for an ~~An~~

isolated antibody that binds specifically to the Hu-Asp polypeptide ~~of any of claims 104-107~~ described herein.

Please replace the paragraph beginning at page 11, line 21 with the following amended paragraph.

The invention provides for a ~~A~~ method to identify a cell that can be used to screen for inhibitors of β secretase activity comprising:

Please replace the paragraph beginning at page 11, line 30 with the following amended paragraph.

~~The method of claim 108 where~~ In one embodiment, the cells are collected and the critical peptide is the APP C-terminal peptide created as a result of the β secretase cleavage. ~~The method of claim 108 where~~ In another embodiment, the supernantent is collected and the critical peptide is soluble APP where the soluble APP has a C-terminal created by β secretase cleavage. ~~The method of claim 108 where~~ In one variation, the cells contain any of the nucleic acids or polypeptides ~~of claims 1-86~~ described above and where the cells are shown to cleave the β secretase site of any peptide having the following peptide structure, P2, P1, P1', P2', where P2 is K or N, where P1 is M or L, where P1' is D, where P2' is A. ~~The method of claim 111 where~~ In another variation P2 is K and P1 is M or ~~The method of claim 112 where~~ P2 is N and P1 is L.

Please replace the paragraph beginning at page 12, line 6 with the following amended paragraph.

~~Any~~ The invention provides for a bacterial cell comprising any nucleic acids or peptides ~~in claims 1-86 and 92-107~~ described above. For example, ~~A~~ bacterial cell ~~of claim 114 where the bacteria~~ that is *E coli*. ~~Any~~ The invention also provides for an eukaryotic cell comprising any nucleic acids or polypeptides ~~in claims 1-86 and 92-107~~ described above.

Please replace the paragraph beginning at page 12, line 9 with the following amended paragraph.

~~Any~~ The invention provides for an insect cell comprising any of the nucleic acids or polypeptides ~~in claims 1-86 and 92-107~~ described above. ~~A insect cell of claim 117 where the insect is~~ These insect cells contemplated include sf9, ~~or~~ and High 5. ~~A insect cell of claim 100 where the insect cell is High 5~~. The invention also provides for a ~~A~~ mammalian cell comprising any of the nucleic acids or polypeptides ~~in claims 1-86 and 92-107~~ described herein. ~~A mammalian cell of claim 120 where the~~ An exemplary mammalian cell ~~is~~ may be selected from the group consisting of, human, rodent, lagomorph, and primate. ~~A mammalian cell of claim 121 where the mammalian cell is selected from the group consisting of human cell. A mammalian cell of claim 122 where~~ the An exemplary human cell ~~is~~ may be selected from the group comprising HEK293, and IMR-32. A ~~mammalian cell of claim 121 where the cell is a primate cell. A~~ An exemplary primate cell ~~of claim 124 where the primate cell is~~ may be a COS-7 cell. ~~A mammalian cell of claim 121 where cell is selected from a rodent cells.~~ A rodent cell ~~of claim 126~~ may be selected from, CHO-K1, Neuro-2A, and 3T3 cells. The invention also provides for ~~A~~ a yeast cell ~~of claim 115, or An~~ an avian cell ~~of claim 115~~ comprising any of the nucleic acids or polypeptides described above.

Please replace the paragraph beginning at page 12, line 21 with the following amended paragraph.

~~Any~~ The invention provides for an ~~The~~ isoform of APP where the last two carboxy terminus amino acids of that isoform are both lysine residues. ~~In written descrip. Define~~ An isoform is any APP polypeptide, including APP variants (including mutations), and APP fragments that exists in humans such as those desribed in US 5,766,846, col 7, lines 45-67, incorporated into this document by reference. One embodiment is an ~~The~~ isoform of APP ~~from claim 114,~~ comprising the isoform known as APP695 modified so that its last two having two lysine residues as its last two carboxy terminus amino acids. ~~The~~ For example, an APP isoform ~~of claim 130~~ comprising SEQ ID NO:16, or the APP ~~The~~ isoform variant ~~of claim 130~~ comprising SEQ. ID. NO. 18, ~~and~~ or 20. ~~Any~~ The invention also provides for an eukaryotic cell line, comprising nucleic acids encoding modified APP isoforms or polypeptides ~~of claim 130-132~~ comprising modified APP isoforms. ~~Any~~ The cell line ~~of~~

~~claim 133 that is~~ may be a mammaliam cell line (HEK293, Neuro2a~~), best plus others~~. ~~A~~ The invention also provides for a method for identifying inhibitors of an enzyme that cleaves the beta secretase cleavabe site of APP comprising:

Please replace the paragraph beginning at page 13, line 11 with the following amended paragraph.

~~The method of claim 135 wherein~~ In an exemplary embodiments, the cultured cells are a human, rodent or insect cell line. ~~The method of claim 136 wherein~~ It is also contemplated that the human or rodent cell line exhibits β secretase activity in which processing of APP occurs with release of amyloid beta-peptide into the culture medium and accumulation of CTF99 in cell lysatesu~~. A method as in claim 137 wherein the human or rodent cell line treated with the~~ Among the contemplated test compounds are antisense oligomers directed against the enzyme that exhibits β secretase activity, reduces release of soluble amyloid beta-peptide into the culture medium and accumulation of CTF99 in cell lysates. A method for the identification of an agent that decreases the activity of a Hu-Asp polypeptide selected from the group consisting of Hu-Asp1, Hu-Asp2(a), and Hu-Asp2(b), the method comprising:

Please replace the paragraph beginning at page 16, line 3 with the following amended paragraph.

Figure 2: Figure 2 shows the nucleotide (~~SEQ ID NO: 3~~ SEQ ID NO: 5) and predicted amino acid sequence (~~SEQ ID NO:4~~ SEQ ID NO: 6) of human Asp2~~(a)~~ (b).

Please replace the paragraph beginning at page 16, line 5 with the following amended paragraph.

Figure 3: Figure 3 shows the nucleotide (~~SEQ ID NO:5~~ SEQ ID NO: 3) and predicted amino acid sequence (~~SEQ ID NO:6~~ SEQ ID NO: 4) of human Asp2~~(b)~~(a). ~~The predicted transmembrane domain of Hu-Asp2(b) is enclosed in brackets~~.

Please replace the paragraph beginning at page 35, line 27 with the following amended paragraph.

Several interesting features are present in the primary amino acid sequence of Hu-Asp2(a) (~~Figure 2~~ Figure 3 and SEQ ID No. 4) and Hu-Asp-2(b) (~~Figure 3~~, Figure 2 SEQ ID No. 6). Both sequences contain a signal peptide (residues 1-21 in SEQ ID No. 4 and SEQ ID No. 6), a pro-segment, and a catalytic domain containing two copies of the aspartyl protease active site motif (DTG/DSG). The spacing between the first and second active site motifs is variable due to the 25 amino acid residue deletion in Hu-Asp-2(b) and consists of 168-*versus*-194 amino acid residues, for Hu-Asp2(b) and Hu-Asp-2(a), respectively. More interestingly, both sequences contains a predicted transmembrane domain (residues 455-477 in SEQ ID No.4 and 430-452 in SEQ ID No. 6) near their C-termini which indicates that the protease is anchored in the membrane. This feature is not found in any other aspartyl protease except Hu-Asp1.